REMARKS

Claims 37-41, 46, and 49-62 are pending in this application. Claims 37-41, 46, and 49-62 have been rejected. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Withdrawn Objections/Rejections

Applicants acknowledge the withdrawal of the rejection to claims 46 and 49 under 35 U.S.C. 112, second paragraph.

II. Rejection of the Claims Under 35 U.S.C. §103

Claims 37-41, 46 and 49-62 have been rejected under 35 U.S.C. 103(a) as being unpatentable over James et al. (U.S. 6,228,401). The Examiner contends that James et al. teach the exact same ingredients as required by the instant claims as well as the use of rotary cutters which is a type of forced-action mixer, which is the same process recited in the instant product-by-process claims. The Examiner acknowledges that James et al. fail to explicitly teach that the size of 50% of the flutamide particles in the pharmaceutical formulation is greater than 26 microns as required in independent claim 37, or wherein 90% of the flutamide particles is greater than 130 microns as required by claim 46, or that the specific surface area less than 0.35 m2/cm3 as required by claim 49. However, the Examiner asserts that it would have been obvious to modify the teachings of James et al. to arrive at the present invention.

Applicants respectfully traverse this rejection. At the outset, Applicants respectfully submit that the finality of

the subject Office Action is premature and therefore requests withdrawal of that finality, pursuant to Section 706.07(d) of the Manual of Patent Examining Procedure (MPEP). As grounds for this Request, Applicants note that the final Office Action has rejected independent claim 41 under 35 U.S.C. 103(a) as being unpatentable over James et al. (U.S. 6,228,401). However, the non-final Office Action that immediately preceded the final Office Action did not reject independent claim 41 under 35 U.S.C. 103(a) as being unpatentable over James et al. Section 706.07(a) of the MPEP specifies the conditions under which the finality of a second or subsequent Office action is proper, providing that:

> Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement….

Applicant submits that the rejection of independent claim 41 is a new ground of rejection. Also, because Applicant neither amended claim 41 nor filed an IDS between the subject non-final and final Office actions, the conditions required by MPEP § 706.07(a) cannot yet be satisfied.

Furthermore, while the instant rejection is stated as being based upon the teachings of James et al., in several instances (page 11, 2nd full paragraph; page 12, 1st and 2nd paragraphs; and page 13, 1st full paragraph) reference is made to the teachings of Jones et al. While this would appear to be an obvious error, Applicant respectfully requests, in accordance with the principles of compact

prosecution, that the Office articulate, on the record and with specificity sufficient to support a *prima facie* case, the factual basis of obviousness. (MPEP §2164.01).

Accordingly, for these reasons alone, as well as the Office's policy of compact prosecution, the finality of the final Office Action should be withdrawn.

Regarding the basis of the rejection of claims 37-40, 46 and 49-62, Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness. James et al. teach that unmilled flutamide readily agglomerates thereby rendering milling difficult (col. 2, lines 46-47). James et al. found that milling of flutamide in the presence of a pharmaceutically acceptable diluent such as a starch, sugar, cellulose derivative, or inorganic salt facilitates the milling of flutamide (col. 2, lines 47-54) and yields X_{50} values of less than 26.0 μm (col. 2, lines 20-25). This reference teaches that flutamide active pharmaceutical ingredient, having such X_{50} values, can be prepared through conventional milling techniques including, *e.g.*, the use of rotary cutters (col. 2, lines 30-38). James et al. further teach that flutamide milled in this manner can be included in a pharmaceutical composition containing common excipients, diluents or carriers such as those described in the paragraph spanning col. 3 and 4 to form tablets, capsules, suspensions powders the like. In this respect, Examples 1-4 of James et al. teach milling of flutamide in the presence of lactose and the use of this milled flutamide to prepare capsule and tablet formulations containing sodium laurel sulfate via a wet granulation method (Examples 6 and 7) or blending (Example 9). Administration of flutamide, milled in the manner described

by James et al. (*i.e.*, having X_{50} values of less than 26.0 μm), was found to achieve blood levels of 2-hydroxyflutamide (the active metabolite of flutamide) consistent with blood levels provided by Eulexin® (col. 4, lines 38-43). In contrast, *similar compositions with X_{50} particle size values greater than 26.0 μm failed to provide 2-hydroxyflutamide blood levels consistent with that of Eulexin®* (col. 4, lines 43-55).

In this respect, Applicants point out that while James et al. teach pharmaceutical compositions comprising flutamide particles and sodium laurel sulfate (as surface-active ingredient) prepared by a wet granulation (Examples 6, 7, and 9; and the paragraph spanning col. 3 and 4), this does not constitute a teaching or suggestion of the instant claim limitation of "wherein the [unmilled] flutamide has been subjected to intensive mixing in a forced-action mixer with the at least one surface-active substance." The compositions of James et al. were prepared in essentially two steps: (1) milling of flutamide in the presence of a pharmaceutically acceptable diluent such as a starch, sugar, cellulose derivative, or inorganic salt that facilitates the milling of flutamide (col. 2, lines 47-54); and (2) formulation of milled flutamide by wet granulation into tablets and capsules with common excipients, diluents or carriers (Examples 6, 7, and 9; and the paragraph spanning col. 3 and 4). The only process of James et al. that suggests the use of a forced-action mixer is the step of milling flutamide in the presence of pharmaceutically acceptable diluents, not a surface-active substance as required by the instant claims. Indeed, even if one were to consider the wet granulation of James et al. as including

intensive mixing in a forced-action mixer, the flutamide used in the wet granulation step is *milled* flutamide, not *unmilled* flutamide as required by the instant claims. Therefore, James et al. do not teach or suggest the instant claim limitation of subjecting unmilled flutamide to intensive mixing in a forced-action mixer with at least one surface-active substance.

According to the instant invention, unmilled flutamide subjected to intensive mixing in a forced-action mixer with at least one surface-active substance produces particles with X_{50} values of greater than 26 µm and a resultant release of 92-100% of the active ingredient (page 17 of the Specification).

On pages 6-8, the Office Action alleges, in part, that it would have been obvious for one of ordinary skill in the art to arrive at an X_{50} value of greater than 26 µm based upon the teachings of James et al. with the motivation for milling/mixing less to arrive at the larger particle size being a reduction in heat degradation of the product. However, this reasoning completely disregards the explicit teaching away by James et al. of doing what the Examiner suggests.

MPEP § 2143.03(VI) states that "[a] prior art reference must be considered in its entirety, *i.e.*, as a <u>whole</u>, including portions that would lead away from the claimed invention." Accordingly, where cited art teaches away from a claimed feature, the cited art is not available for the purposes of an obviousness rejection.

In the instant case, James et al. not only fail to teach or suggest an X_{50} value of greater than 26 µm, but further teaches away from this limitation. Specifically,

James et al. indicate that flutamide compositions with X_{50} particle size values greater than 26.0 µm failed to provide 2-hydroxyflutamide blood levels consistent with that of Eulexin® (col. 4, lines 43-55). Arguably, as in the present invention, the whole of the teachings of James et al. is concerned with increasing the solubility and bioavailability of flutamide. As such, there is simply no rationale to increase particle size as the Examiner suggests, because James et al. provide a clear demonstration that doing so would decrease the bioavailability of the active ingredient. Therefore, James et al. teach away from the present invention because this reference suggests that the developments flowing from its disclosures are unlikely to produce the objective of Applicants' invention (see *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)).

In so far as James et al. discourages the use of flutamide particles having X_{50} value of greater than 26 µm (see MPEP § 2143.03(VI), quoting *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004)), one of ordinary skill in the art would not modify James et al. in an effort to arrive at the claimed invention.

Furthermore, while the Examiner asserts that the instant claims are product-by-process, wherein the ingredients of the compositions of James et al. are the same as those presently claimed, the courts have held that the structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to

the final product. See, *e.g.*, *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979) (holding "interbonded by interfusion" to limit structure of the claimed composite and noting that terms such as "welded," "intermixed," "ground in place," "press fitted," and "etched" are capable of construction as structural limitations.)

In this respect, it is well-established in the art that the term "unmilled" imparts physical and structural characteristics of flutamide. For example, James et al. teach that "unmilled flutamide has a consistency which readily agglomerates rendering milling difficult with inconsistent results." Col. 2, lines 46-48. As Applicants have appreciated, subjecting unmilled flutamide to intensive mixing in a forced-action mixer with at least one surface-active substance imparts distinct structural characteristics to the final product, *i.e.*, release of 92-100% of the active ingredient (page 17 of the Specification) and an X_{50} value of greater than 26 µm, a feature which is specified in the instant claims. In so far as the pharmaceutical compositions of James et al. have flutamide particle X_{50} values of less than 26.0 µm, the structural characteristics of the instant composition are distinct from the compositions of James et al.

While the Examiner has focused on the motivation to optimize bioavailability by experimenting with particle size distribution and the surface area of resultant particles (page 7 of the Office Action), the Examiner has failed to consider all words in the instant claims, and interrelationship of the same, when judging patentability. See MPEP 2143.03. Specifically, the Examiner has not given proper consideration to the claim limitation of subjecting

unmilled flutamide to intensive mixing in a forced-action mixer *with at least one surface-active substance*. Nowhere does James et al. teach or suggest that a surface-active substance is a critical variable to be considered in the optimization of flutamide bioavailability. Indeed, without the insight provided by the instant specification, there would be no rationale in view of the teachings of James et al. to subject unmilled flutamide to intensive mixing in a forced-action mixer *with at least one surface-active substance* as claimed. In this respect, the rejection falls into the first error identified in *O'Farrell*, in which "what would have been 'obvious to try' would have been to vary all parameters or try each of number possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). As upheld in *Abbott Laboratories v. Sandoz, Inc.* (Fed. Cir. 2007), "the obviousness of selection of components, when there is no prediction in the prior art as to the results obtainable from a selected component, differs from the issue in *KSR*, where the Court provided guidance that 'a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.'" 127 S. Ct. at 1740.

The present invention cannot be viewed as a predictable result of modifying the teachings of James et al. because it was not known prior to the present invention that surface-active substances had any influence on the particle size or bioavailability of flutamide. Indeed, in view of the large

number of possible elements in pharmaceutical compositions, including the vast number of active ingredients and infinite number of excipients, carriers and the like, there would be no reasonable expectation of successfully obtaining the claimed composition by varying all the parameters of a pharmaceutical composition to arrive at those presently claimed.

The Examiner's broad-brush approach and unfounded assumptions were condemned in *Graham v. John Deere Co.*, where it was recognized that the obviousness inquiry must "guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue." 383 U.S. at 36, 86 S.Ct. at 703. There are a myriad of possible elements in pharmaceutical compositions, such that the "known options" in the prior were not "finite, identified, and predictable," the words of *KSR* (550 U.S. 398 (2007)). Only with the Applicants' educated application of what was known in the art and intelligent exploration of what was not known did Applicants appreciate the benefit of subjecting unmilled flutamide to intensive mixing in a forced-action mixer with at least one surface-active substance during the process of preparing a pharmaceutical composition containing flutamide.

For the reasons above, Applicants have identified reversible error in the Examiner's determination of obviousness under 35 U.S.C. 103(a) and respectfully request that this rejection be reconsidered and withdrawn.

Claim 41 remains rejected under 35 U.S.C. 103(a) as being unpatentable over James et al. in further view of Neri et al. (US 3,995,060). It is suggested that while James et al. fail to teach that flutamide has been subjected to

recrystallisation as necessitated by claim 41, Neri et al. compensate for this deficiency in the teachings of the primary reference.

Applicants respectfully traverse this rejection. MPEP 2143.03 clearly indicates that if an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). In this respect, for the reasons stated above, Applicants respectfully assert that base claim 37 is nonobvious in view of James et al. As such, claim 41, which depends from claim 37, is also nonobvious. It is therefore respectfully requested that these rejections under 35 U.S.C. 103(a) be reconsidered and withdrawn.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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